Modeling of TREX1-Dependent Autoimmune Disease using Human Stem Cells Highlights L1 Accumulation as a Source of Neuroinflammation.

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Public Summary:
On this work, we modeled a rare neurological auto-immune disease called Aicardi-Goutieres Syndrome (AGS), caused by mutations in the TREX1 gene. AGS is characterized by a dramatic neuronal loss, leading to a life-long disability condition. The lack of robust animal models has blocked the understanding of the pathology and potential treatments. Using pluripotent stem cells, we create the first human model of AGS. When these cells were differentiated into neurons, we observed a massive cell death. On the other hand, astrocytes derived from the same donor cells survived, but displayed a clear inflammatory reactivity response by releasing interferon. We showed that the interferon response from astrocytes was affecting neuronal survival. When investigating the causes of the inflammatory response, we focused on the accumulation of nucleic acid on the cytoplast of astrocytes. The identity of these nucleic acid was LINE-1 retrotransposons. LINE-1 or L1s are repetitive sequences on the human genome that can autonomously retrotranspose using reverse transcriptase. To prove that astrocytes were recognizing L1s as intruders, we treated these cells with HIV reverse transcriptase inhibitors. The treatment not only reduce the inflammatory response, but also rescued neuronal death. More importantly, we also treated brain organoids carrying TREX1 mutations and we could rescue the microcephalic phenotype, revealing a novel therapeutic opportunity for AGS.

Scientific Abstract:
Three-prime repair exonuclease 1 (TREX1) is an anti-viral enzyme that cleaves nucleic acids in the cytosol, preventing accumulation and a subsequent type I interferon-associated inflammatory response. Autoimmune diseases, including Aicardi-Goutieres syndrome (AGS) and systemic lupus erythematosus, can arise when TREX1 function is compromised. AGS is a neuroinflammatory disorder with severe and persistent intellectual and physical problems. Here we generated a human AGS model that recapitulates disease-relevant phenotypes using pluripotent stem cells lacking TREX1. We observed abundant extrachromosomal DNA in TREX1-deficient neural cells, of which endogenous Long Interspersed Element-1 retrotransposons were a major source. TREX1-deficient neurons also exhibited increased apoptosis and formed three-dimensional cortical organoids of reduced size. TREX1-deficient astrocytes further contributed to the observed neurotoxicity through increased type I interferon secretion. In this model, reverse-transcriptase inhibitors rescued the neurotoxicity of AGS neurons and organoids, highlighting their potential utility in therapeutic regimens for AGS and related disorders.